INFLUENZA
AND
ITS
TREATMENT.

BY
JAMES DAVIDSON MILL.

ADELAIDE
SOUTH AUSTRALIA.

JULY
1939.

Influenza, spoken of till quite recently as "the most puz- (1)
zling of all infectious diseases", has been finally proved (2 to 7)
to be due to a virus. This is 80 millemicrons in size and
is thus so small that it is immaterial whether it be class-
ified as animate or inanimate, so some consider it to be (8)
enzyme in nature. "There is a possibility of its having
a spontaneous evolution within the mucous membrane under
suitable conditions, such as humid air and draughts and
it is propagated by the transmission of specific enzymic
proteins from one organism to another-mainly through the
impinging of such colloidal particles upon the mucous
membrane of the nose and throat, leading by catalysis to
the rapid transformation of inactive fibrillar gel proteins
into active enzymic proteins in a sol condition- and con-
sequent physiological changes characteristic of influenza" (9)
It is spread very rapidly, so in pandemics "we may have
three cases reported on one day and three thousand the
next". The evidence shows that there are very many different (10)
strains of this virus. "The multiplicity within the group
recall to some extent the multiplicity of micro-organisms
comprised within the "Flexner" group of dysentery bacilli" (11)
"Like other viruses that of influenza is cytotropic and
does not multiply in body fluids but only in the presence
of living cells and like swine fever and measles the virus
appears to cause mild lesions but paves the way to second-
ary infections which may produce very serious lesions."
"It seems probable that influenza is caused by a filterable
virus which depresses the resistance of the body to an
unparalleled degree, so that secondary invasion by Pfeiffers
bacillus and other organisms may occur and lead to a fatal
pneumonia." (12)
"An acute disease characterised by fever, prostration, a
great liability to pulmonary complications, and an epidemic
incidence. Nothing is known of the predisposing causes
except that the disease tends to recur in pandemics about
every forty years and in epidemics about every thirty
three weeks." (13)
"The micro-organisms most commonly found in association
with influenza are Pfeiffers bacillus, streptococci of a
haemolytic kind, pneumococci, micrococcus catarrhalis, and
staphylococci. It seems certain that most of the fatal
cases owe their lethal character to virulent streptococci." (14)

Clinical Picture. (Scadding) (15)
"The onset is characterised, in most cases, by a sudden prostration; headache, shivering and pains in the back and limbs are the commonest early symptoms. Occasionally the onset is dramatically sudden, with a fainting attack. In a minority of cases a more insidious onset after a day or two of general illness is observed, and in a small minority there may be a history of slight coryza for several days before the sudden onset of prostration and other definite symptoms-pain behind the eyes on moving them or in a few cases photophobia- occur at the onset in a proportion of cases, but cough, coryza and sore throat are initial complaints in only a few.
Symptoms of the fully developed disease.
Malaise is constant and in many instances is accompanied by apathy and a desire to be undisturbed. Headache is a constant symptom, and is frequently frontal. Anorexia is almost constant and may be extreme during the febrile period. Shivering may occur, but is rarely sufficient after the onset in an uncomplicated case to amount to a rigor. Dizziness on assuming the erect position is a common symptom. Muscular pains in the back and limbs and the ocular symptoms which may be present at the onset are more frequent during the course of the disease. A mild coryza may be present at the onset but this symptom reaches its maximal incidence on the second or third day, often accompanied by nasal obstruction, it is then present in about three out of four cases. The coryza is rarely severe and never assumes the form of a streaming "cold in the nose" Cough, while not common actually at the onset, develops within a short time in the majority; it is frequently accompanied by a painful sensation behind the sternum. At first it is usually unproductive, but later scanty muco-purulent sputum is produced in about half the cases. The cough is often one of the last symptoms to disappear. Throat symptoms are not prominent at the onset, dryness and discomfort rather than soreness being usual. In some cases, complaint of sore throat is not made until the third or fourth day, and in about half the cases this symptom never occurs. Nausea and vomiting are occasionally observed on the first and second days.
Gastro-intestinal and nervous forms of ifluenza have been described but the study of the 1936-37 epidemic did not support the view that these manifestations are separate entities. Although anorexia was present in nearly all patients, and nausea and vomiting sometimes occurred these symptoms were always accompanied by and subsidiary to the other symptoms of the disease.

" Similarly, though the headache was constant, and the mental apathy often striking, and fainting often occurred at the onset, these symptoms were never so conspicuously related as to constitute a special nervous form of the disease.
Pyrexia.-In uncomplicated cases, the duration of the fever averages three or four days. The height and type of the fever vary and have no constant relationship to the severity of the symptoms. It is interesting to note that in the ferret the fever of influenza commonly has a duration of about four days, and is characterised by two peaks with a remission or intermission between; this type of temperature response is observed in only a minority of human cases. The pulse rate has frequently been said to be slow in epidemic influenza; in the 1936-37 outbreak this feature was not detected.
Physical signs.-The general aspect at the onset is constant. A generalised flushing of the face often affects especially the ears, and the lips may present a slightly cyanosed appearance. The eyes show conjunctival injection often some lachrymation, and the lids frequently appear heavy and drooping. The general apathetic attitude of the patient is notable. The pyrexia is associated with some sweating, but this is rarely excessive apart from the effects of therapy.
The pharynx is notewothy chiefly for the slightness of the changes observed. There is usually some general injection, affecting the posterior part of the fauces and the posterior pharyngeal wall. There is often some swelling of the adenoid tissue in this region, so that the lymphoid follicles on the posterior pharyngeal wall appear prominent.
In about half the cases a peculiar dryness of the posterior pharyngeal wall is observed on the second and third days; this may present a glazed appearance or it may appear dull and granular. It is most exceptional to find gross changes in the tonsils which merely take part in the general injection of the pharynx; follicular exudation is practically never observed. Cervical glandular enlargement also does not occur in uncomplicated cases.
The lungs may show abnormal signs on careful examination in some cases showing no symptomatic evidence of specially severe involvement of the lower respiratory tract. In some these signs are not specially characteristic, consisting only of occasional rhonchi or a few basal rales. In a few cases, more significant signs are found; these consist of localised and constant areas of weak or even absent breath-sounds, usually at the bases.

"In uncomplicated cases this sign disappears in two or or three days,but sometimes when the breath sounds return they are accompanied in the previously silent area by moist inspiratory rales,which may persist for a week or ten days.Since these signs are not accompanied by radiographic changes,it is probable that they are due to a localised bronchiolitis.The types of lung lesion that may be an accompaniment or sequel of influenza are confusing in their variety.The more severe lesions can be divided into three main groups.

The first may be described as"bronchiolitis"The less severe cases of this group present nothing more than an unusual prolongation of cough and expectoration with persistence of physical signs in the lungs of the type described in connection with uncomplicated cases.At the other end of the scale are patients who become dyspnoeic and cyanosed and present physical signs suggesting oedema of the bases of the lungs,short of actual consolidation with a generalised bronchitis.In these there is impairment of percussion note at the bases,with weak breath sounds,numerous rales,and diminished voice conduction in these areas,and frequently scattered rhonchi audible over the rest of the lungs.All gradations of severity between these two extremes may be observed.

The second group consists of cases in which more or less extensive areas of consolidation appear,either in addition to "bronchiolitic"changes of any grade of severity or occasionally in the course of a case which has not previously shown abnormal lung signs.In some of the cases of this group there is a definite onset of "pneumonic"symptoms with pleurisy and rigor or increased dyspnoea,usually about the third to the sixth days but occasionally later.The physical signs of the consolidations frequently differ strikingly from those found in primary pneumococcal pneumonia.Dullness over the affected areas is extreme,breath sounds vary froma weak tubular or bronchial character to complete absence,and the voice conduction is often aegophonic or diminished rather than increased.In these cases the temperature chart may bear little relation to the clinical state of the patient.Resolution of large areas of consolidation is usually slow.

The third group ,which is fortunately rare except in pandemics,is that of the fulminating pneumonias.In a case of this type,the symptoms rapidly progress from the onset of the influenza,the patient becomes dyspnoeic,with a grey or lilac cyanosis,apathetic and collapsed,and dies within two or three days.

"There is no doubt that bacteria play an important part in these lung changes. In the 'bronchiolitis' group, the organisms commonly associated with pneumonia are seldom present in the sputum; in the second group, with definite consolidations, organisms of this type are frequently found predominating in cultures of the sputum. In cases that come to necropsy, pathogenic bacteria are, almost without exception, found in the lungs; during the 1936-37 epidemic, in three cases of fulminating pneumonia both virulent bacteria, which in these instances were Staph. Aureus and the influenza virus were demonstratedin the lungs removed at necropsy. In the lungs of patients dying of lung complications later in the course of the disease it was not found possible to demonstrate the virus. (7)
It seems likely that the lung changes in human influenza are the resultant of both bacterial and virus invasions. The pure virus infection may be responsible for the whole of the clinical picture up to the stage of bronchiolitis with basal oedema. Bacterial invasion may modify the picture in various ways; it may alter the type of , and prolong an influenzal bronchitis. It may assist in producing a patchy lobular pneumonia. A more virulent bacterial infection in a similar case may proceed to lobar consolidation And, finally, the acute fulminating pneumonias are probably produced by extensive virus damage with simultaneous bacterial infection of a virulent nature.
Thus, the course of the disease depends upon the extent and virulence both of the virus and of the bacterial infections; the extraordinary variations of the clinical picture is due to the numerous possible combinations of these factors. (16)
Differentiation of Influenza from epidemic 'febrile catarrh'.
This differentiation may be possible on clinical grounds.
1. The form of the epidemic is more clear cut in influenza It appears suddenly and rises rapidly to a peak. There is a greater uniformity in the clinical aspectof the uncomplicated cases in an epidemic of influenza.
2. The onset of symptoms is more often sudden in influenzal cases, and premonitory symptoms are less common. The earliest syptoms are constitutional with severe prostration, headache, shivering, and muscular pains. Catarrhal symptoms-coryza and cough- are less prominent and develop later in the disease than in febrile catarrhs in which they are often the earliest symptoms. Sore throat is a less common early complaint in influenza.

"3.Onexamination,obvious acute inflammatory changes in the fauces and pharynx are less frequent in influenza; exudation on the tonsils is rare.The Characteristic dry pharyngitis,when present,is a valuable sign.
4.In the lungs,the characteristic areas of "suppressed" breath sounds occurring in a small number of patients otherwise indistinguishable from the rest,are suggestive of influenza.
5.If facilities are available,a positive diagnosis of influenza may be made by demonstrating the virus.Suitable material for inoculation into ferrets can be obtained by instructing the patient to gargle with about 15 cc of sterile saline,and to spit the garglings into a sterile vessel containing a little broth.This should be kept in the cold if there is any delay in its transmission to the laboratory.Virus is likely to be demonstrable in the first three days of the illness only.The virus has been demonstrated in the lungs of patients dying of acute fulminating pneumonia within the first few days of the onset,but not in lungs of patients dying after more prolonged illness.The only other way of making a definite diagnosis in the laboratory is by comparison of the virus neutralising power of serum taken during the acute stage and in convalescence.A substantial rise may be taken as diagnostic.
The convalescence from influenza has usually been stated to be characterised by mental depression.This was not prominent in the 1936-37 epidemic.
There is often a tendency to bradycardia during convalescence.The tendency to the late development of serious pulmonary complications even up to the fourteenth day from the onset shows that a true return to normal health is delayed for a long time after the disappearance of obvious symptoms.
Complications,such as tonsillitis,otitis media,and nasal sinusitis are all rare and are probably the result of secondary infections facilitated by a generally reduced resistance.
Blood count.-Examination of the blood is not of positive diagnostic value.

" The treatment of influenza.
In the absence of specific treatment, the most important points in the treatment of influenza are adequate rest and nursing care. It should be urged that all patients with influenza should be kept in bed until the temperature has been normal for at least two days after an uncomplicated attack, and should than spend a week or ten days quietly convalescing before returning to their normal activities. If it had been possible to confine the term "influenza" in the past to the virus disease, this advice would not seem so Utopian; the habit of referring to so many trivial disorders under this title has tended to minimise in the minds of the public the seriousness of the disease to which it properly belongs. The reason for the long convalescence has already been indicated; a greatly reduced resistance of the respiratory tract to bacterial invasion may last for as long as two or three weeks after a simple influenzal attack, and in an epidemic it is frequently observed that the symptoms of a pneumonic complication first appear a day or two after early resumption of normal activities. There is no evidence that any drug influences the course of the disease. In the 1936-37 epidemic, it was observed that treatment with salicin, with sodium salicylate, and with aspirin and potassium citrate in different localities produced no significant alteration in the duration of pyrexia as compared with that observed in patients receiving the minimum of treatment. It is clear therefore that drug therapy can only be symptomatic. Some patients are made more comfortable with aspirin and in these it may be administered in doses of 10-15 grs. fourhourly; in some patients this drug causes such severe sweating that it actually increases their discomfort and should therefore be avoided. If there is sleeplessness a simple hypnotic, such as Dovers powder, 15 grs. or medinal 7 grs. with aspirin 15 grs. is all that is necessary. Constipation is common, but there is usually no need to disturb the patient with measures for the treatment of this symptom in the first day or two of an acute attack when little is being taken by the mouth; after this a simple laxative such as senna or cascara will usually suffice; if constipation is troublesome an enema is the best treatment. The treatment of the pulmonary manifestations does not come within the scope of this article.

" Specific treatment has been brought nearer to realization by the discovery of the etiological agent.It has proved possible to prepare from horses an anti-viral serum which has a therapeutic effect in experimental animal infections.From the point of view of practical therapeutics this is at present only an indication of possible future line of advance.

Specific prophylaxis.

The hope of attainment of prophylactic vaccination is less remote.It has been established that in ferrets recovered from an infection there is a rise of antibodies in the serum,which slowly wanes.The animal is completely resistant to reinfection for about three months.Virus injected subcutaneously produces in a normal animal an increase in antibodies,some increase in resistance to infection, and a modification of the attack if infection occurs and in previously infected animal whose resistance has waned ,a restoration of full immunity.It has been found that virus inactivated with 1-5000 formaldehyde can produce these effects.The source of a virus may be mouse lung affected with a pure influenza virus pneumonia,or virus grown on tissue cultures of chick embryo.In this country formalin inactivated material and in the United States living virus have been used in human observations.A definite rise in serum antibodies has been observed after subcutaneous injection in man of either of these types of material.No convincing observations on the practical value of this form of vaccination,made under well controlled conditions,have as yet been made possible.The chief difficulty in making such observations is that the rise in antibodies takes a week at least to develop and wanes within a few months;it is therefore extremely difficulty to ensure that the time of the increased immunity coincides with the appearance of an influenza epidemic.Another possible difficulty arose when it was discovered that there are distinct strains of influenza virus,which are not antigenically identical,so that an animal vaccinated with one strain may show a relatively poor rise in antibodies to another.There are thus many problems to be solved before prophylactic vaccination of man comes into the realm of practical therapeutics." (18) (51)

That these are being solved is shown by more recent work, where it is stated that a"double-phase intrinsic cyclical theory,modified from Brownlee's single-phase theory with a seasonable factor,is presented as accounting for all the main phenomena of influenza epidemicity."And so"prophylactic measures should be adopted,then,for the highly susceptible before each of the 3½ monthly periods and more widely before a major epidemic is probable,as in February 1941." (20)

Again with regard to treatment we find it stated"That so many of the fatal cases seem to be so because of virulent streptococcal toxaemia that some authorities give anti-streptococcal serum in all bad cases.Many experimental methods of treatment were exploited in the pandemic of 1918-19,including a large range of antiseptics by the intavenous route,but no remedy emerged from these trials with sufficient credit to merit a reference here" (21)
Another text-book says of influenzal pneumonia"that there is no specific remedy,in a controlled series of cases massive doses of salicin,repeated intravenous injections of 1 cgm.of perchloride of mercury in 1 cc of water and the prophylactic mixed vaccine have been tried without anu beneficial results.The best effects were obtained with the perchloride of mercury." (22)
In the 1918-19 pandemic Lorraine Smith tried different intravenous injections without success.Later in London mercurochrome was given intravenously in septicaemic conditions but did not fulfil its promises.
Still Dr Goodall in Edinburgh has found intravenous colloidal iodine of such help in treating pneumonias that it is used always in his wards.So we see that all along an endeavour has been made to find a bactericidal agent to help in the treatment of the secondary infections that occur with influenza and which have proved so fatal.
Till sulphanilamide and its derivatives appeared no such bactericidal drug had been discovered;and with its introduction a powerful weapon has been given us with which to fight certain invading organisms.
The summing up of the pharmacology of sulphanilamide and its compounds given by Buttle recently shows that there are two classes of compounds. (23)
"The drugs of the first class where the amino group is substituted are the original prontosil,rubiazol,proseptasine and soluseptasine.It is probable that all these substances owe their activity to their splitting up in the body into sulphanilamide and an inactive substance,although this cannot be regarded as finally proved.The activity of this class of substances,where the amino group of sulphanilamide is substituted by other groups,is no greater than,and in some cases not so great as,that of the sulphanilamide itself.The drugs of the second class of sulphanilamide derivatives,where substituents are introduced into the amide group,are uleron,albucid,and M & B 693;unlike the substances of the first group these do not appear to be broken down to sulphanilamide in the body but probably are themselves the active agents.

" M & B 693 represents a considerable advance in chemotherapy with these compounds.It is active against all types of pneumococci,whereas sulphanilamide is effective only against type 3.Good results in pneumonia have been now (24.25)
reported by a number of authors and there are accounts (26.27)
of successes in pneumococcal meningitis.Experimental work has shown that some types of pneumococci are resistant,these do not belong to any one serological (28.29)
group;a further observation of great interest is that susceptible pneumococci can be rendered resistant by successive passages through treated mice.Staphylococcal infections in mice are influenced more by M & B 693 than (30)
by sulphanilamide,and there are a few reports of cures (31.32)
of clinical staphylococcal septicaemic conditions.The (31.33)
advantage of the compound in staphylococcal infections is not so great as in the case of pneumococcal infections but it is undoubtedly the best drug to use in these cases.
In meningococcal meningitis clinical reports indicate (34.35)
that it is very active but no comparison with sulphanilamide has as yet been made.In experimental streptococcal
infections it is as active as sulphanilamide or a little (32.36)
more active;but there is no clinical report,as yet,in which the two drugs are compared.In experimental infections with vibrion septique and bac.Welchii preliminary experiments indicate that it is more active than sulphanilamide, although the effect is even better when combined with serum treatment.A temporary improvement has been obtained in cases of infective endocarditis. (36)
It thus appears that M & B 693 is effective whenever sulphanilamide is effective and is also active in certain conditions where sulphanilamide fails.It is probably the drug of choice for any severe case of pyrexia where the bacteriological diagnosis is doubtful,also it is the most potent one in pneumococcal,staphylococcal and gonococcal infections.When the condition is known to be a [illegible]-coccal or meningococcal infection it is still an open question as to whether sulphanilamide or M&B 693 should be used.
Absorption and excretion of these drugs has been studied fully only in the case of sulphanilamide itself but some data are available for the compounds.Sulphanilamide is absorbed very rapidly when taken by the mouth; the concentration in the blood is maximal in about three hours thereafter dropping gradually to zero in the next twenty (37)
four hours.The drug is absorbed entirely from the small intestine and not from the stomach.It is very readily diffusible and finds its way rapidly into all secretions and tissues of the body in almost equal concentration, the concentration in bone and fat is,however, less than elsewhere.The concentration in the cerebro-spinal fluid is nearly as great as that in the blood.There appears to be no good evidence that the drug fails to reach the fluid

" in diseased conditions, although the concentration is found to be very variable from patient to patient; a (38)
factor which will be even more noticeable with M&B693 probably. The drug seems to be selectively absorbed on to the corpuscles of the blood for the concentration here is 50% greater than in the plasma. About 20% of the drug (39)
in the blood is in the acetylated inactive form, and in some cases this proportion may be as high as 40%.
These differences do not seem to be correlated with the therapeutic efficiency of the drug in different subjects. (39)
Sulphanilamide is excreted in part as the free base and partly in the inactive acetyl form; the rate of excretion (40)
is slower in subjects with renal damage. So far as can be (37)
ascertained at present the drug does not undergo any other change in the body; for 90% of the total sulphanilamide given to mice can be found in the urine either as sulphanilamide or as acetyl sulphanilamide. (41)
In the urine the acetyl form accounts for over 50% of the total sulphanilamide, and the rate of excretion follows the urine flow, not the concentration on the plasma. The explanation of this seems to be that the drug is reabsorbed in the kidney tubules, after filtration through the glom- (40)
eruli. The dependence of the rate of elimination on the urine flow makes it possible to wash out the drug by promoting diuresis. In order to obtain the best therapeutic effect it appears to be necessary to maintain a constant concentration of the drug in the blood.
M & B 693 is absorbed and excreted more slowly than sulphanilamide in animals. It reaches the cerebro-spinal fluid but more slowly than sulphanilamide. M & B 693 is excreted in the urine partly as the free base and partly in the inactive acetylated form. For cases of pneumonia 5 grammes in the first twelve hours and 1 gramme four-hourly for a period of a week is recommended." (32)
Nothing has been definitely proved yet in spite of much research work on the exact way that sulphanilamide and its derivatives have their action on infections. So it has been found that sulphanilamide drugs do not stimulate leucocytosis, nor do they influence the quality, quantity (43)
or rate of formation of specific antibodies to pneumococci.
Accordingly it would appear that while it is under the influence of the drug the body behaves towards particularly highly virulent organisms much as the normal body does to those of non-pathogenic type, which are gradually destroyed. No evidence has been found also that stimulation of the reticulo-endothelial system occurs. On the other hand

an attempt to explain the action as an interference with the destruction of hydrogen peroxide formed during the growth of the organism by catalase has been proved wrong Type 3 streptococci(Griffiths) which fail to produce this peroxide being fully susceptible to the action of sulphanilamide. (44)

" With regard to the possible mode of action of sulphanilamide, though no definite statement can be made, it would appear that it acts by a direct bacteriostatic action on the organism, slowing down its growth and consequent production of toxic substances, thus allowing a greater relative effectiveness of the defence mechanism of the body." (45)

Though some benefit has been reported in treatment of distemper, trachoma, lymphogranuloma inguinale and smallpox, the action of sulphanilamide and its compounds has been accepted as of little value other than on the secondary invading organisms. (46)

Once the patient is infected it seems probable that sera chemicals and drugs will be unlikely to affect the course of virus diseases from their essentially cytotropic characteristics. (8)

Vaccines will take time to be introduced because of the many strains of the virus that are being discovered. "We must visualise the probability that immunisation against influenza, using the term in its clinical sense, might involve the use of a vaccine composed of numerous strains of the virus." Prof. Tulloch mentions ten strains in his recent work on the influenzal virus. (47)

Though no direct effect is found in treating measles with sulphanilamide yet there seems little doubt that the pneumococcal and other complications are prevented by its use. (48.49)

From what has been said already it appears that the use of sulphanilamide and its compounds in the treatment of influenza should prove of great value as the worst cases of influenza appear to be so because of the secondary invading organisms, the commonest of which are susceptible to sulphanilamide and its derivatives. Though little difference is to be expected in the actual virus part of the disease.

There occurred here in Adelaide in July 1939 an outbreak which clinically was very like the outbreak of influenza described by Scadding and given above in detail for that reason.

Some sixty cases were seen and noted. Half were treated by the ordinary drugs depending on what symptoms were most in evidence and the other half were given M & B 693 or sulphanilamide in the hope that some comparison could be made.

The name, age, sex date number of days ill before being seen, temperature and other main symptoms were tabulated along with the treatment, number of days till patient was improved and the temperature normal, and the number of days till all symptoms had disappeared.
Those tables on comparison show that the treatment with Sulphanilamide and its derivatives will in most cases shorten the attack and lessen the severity of the symptoms.
Though I have no evidence other than clinical that these cases were true influenza virus infections, the virus was found during this epidemic in Melbourne and the M.O.H. for Adelaide sent a circular to all local doctors that bad cases would be admitted to the Hospital for infectious diseases, where alone these cases were to be sent.
The epidemic was mild and short-only lasting for some two months-highly infectious, most people coming in contact having it in some form, often very mild, and it fitted in with the description of the true virus disease as given above rather than that of a "febrile catarrh".
Most of the cases I saw were mild and though the virus part of the disease did not seem to be influenced by any treatment, yet some half dozen of the worst cases, whose severity was due to invasion of secondary organisms responded in a way that was very gratifying.

Case 48.
This girl aged 18 years complained only of aching pains and headache. She had a temperature of 99 and never developed any complication at all and yet in spite of sulphanilamide she ran a temperature for 5 days and took 9 days to get well.
She was a case, probably, of pure virus infection with no secondary invaders.

Case 31.
This occurred in a man of 75 years who had been ill for two days before I saw him. He was then very weak and ill. Temperature 103, aching all over, with headache and some delirium. He coughed incessantly with a dry unproductive cough. His heart was feeble and his pulse poor. No sign of catarrh was present and he made no complaint of sore throat or sickness. He was so weak that he could not move in bed himself and was incontinent.

Case 31(contd)
His lungs showed no signs of extensive consolidation, only some impairment of percussion note at the bases, with basal rales and patches of absent breath sounds. His sputum was bloodstained for the first two days. He was put on M & B 693 2 tablets every 4 hours for the first two days and then 1 tablet 4 hourly for the next 4 days. An injection of strychnine 1/30 gr. was also given about every 6 hours for the first few days. Later when he had improved, which he did from the start, he was put on a strychnine mixture. He was not well for about six weeks, but, apart from a healing bedsore and some swelling about his ankles was as well then as he had been for years.

Case 43.
This old lady, 81 years of age, seen after two days of illness was also ina very weak state, with aching pains, headache, inflamed dry throat and incessant cough. Her heart sounds were feeble and her pulse was poor and quick. Temperature 102. She was sleepless and delirious when seen and there seemed very little hope of her getting better. Her lungs showed some absent breath sounds, some dullness and rales at the bases and scattered rhonchi over the rest of the lungs. After two days on M&B 693, 2 tabs every 4 hours she began to imrove and took some nourishment. The tablets were continued for a few more days at half the original dose and her improvement was maintained. Later she had a strychnine mixture and was herself again in about 3 weeks time. She had also at the beginning of her illness a few hypodermic injections of strychnine grs 1/60 and a linctus of Syr. coccilana co. to relieve her cough.

Case 45.
A man of 60 years of age who had been subject to asthma for some years. He had been ill for about two or three days before being seen and then was in a serious condition. Temperature 103, cyanosed and very short of breath, with headache, sore throat and incessant cough, he had been sitting up in a chair for two nights with no sleep and no food since his illness began. His pulse was weak and quick the "musical box" sounds in his chest obscured other signs but no consolidation could be found. He was started on M&B 693 but was sick and could only take 1 tablet every 4 hrs. After an injection of 10 mins of adrenaline, 1/100 atropine and 1/30 strychnine he improved somewhat and his improvement was maintained. He also required 3 drs. of paraldehyde before he could sleep and later was put on a mixture containing paraldehyde in it. Altogether he had 3 dozen tablets of M & B 693 and, though his temperature did not fall for four days, he admitted that he was easier in his breathing and his sputum was less purulent than it had been for months.

Case 54.
This case was that of a little girl who had been ill for a week after being in contact with some cases of influenza Though she had been in bed she was still running a temperature of 102 with headache, coryza, sore throat, ulcerated mouth, and a dry useless cough. She was off her food and had been sleeping badly, and had shown no improvement on ordinary medicines. On taking sulphanilamide ½ tablet every four hours she immediately improved and was well in three days time, her temperature dropping to normal in the first 24 hours of treatment. Her chest showed little on examination apart froma few scattered rhonchi.

Case 58.
When seen on the second day of her illness this woman aged 45 years, was in considerable distress. Temperature 104 with aching pains all over, a dry useless cough and pain behind the sternum and marked shortness of breath. Her pulse was quick and poor. Apart from some diminution of breath sounds and some rales at the bases nothing was found on examination of the chest. The throat was sore and on inspection appeared very red, but no exudation was present. She was given sulphanilamide 2 tablets every four hours for two days and then 1 tablet t.i.d for four days and improved at once. All her anxiety disappeared with her temperature in 24 hours and though her cough was still troublesome for over a week, in spite of taking soothing linctus-syr. codeia- she was able to get up in about ten days.

Case 59.
This man, aged 66 years, had been ill for a few days before he was seen. He was then in a serious conition, pale, short of breath, semi-comitose, with a dry cough, incontinent, unable to raise himself in bed and refusing all food. His sputum was scanty, purulent and showed some blood staining at first. Pulse was weak and quick and heart feeble. Lungs showed impairment of percussion note at bases with rales and bronchial breathing, while absent breath sounds and scattered rhonchi occurred elsewhere. He was then given an immediate injection of adrenaline, atropine and strychnine and 2 tablets of M & B 693 every 4 hours started. That night he had rallied somewhat and the hypodermic injection was repeated. On seeing him the next morning the improvement was incredible and he required no more hypodermic injections and made a good recovery in about ten days.

No.	Name.	Sex.	Age.	Date.	Days ill before seen.	Temperature	Musc.pains	Headache	Coryza	Throat	Cough	Gastric	Nervous.	Treatment	Days till temp. normal -better.	Days till cured.	Remarks.
1.	Hancock	M	50	26 Jne.	1	100	P	P	A	P	P	A	A	mist.Tuss. -mist Bark.	7	14	
2.	Elphick	M	10	26	2	103	P	P	A	P	P	A	A	mist.Tuss.-mist Scill.Co	5	21	
3.	Hancock	F	12	1 Jly.	1	100	A	P	P	A	P	A	A	mist.Tuss.	4	7	
4.	Foote	F	40	2	2	101	P	P	A	P	P	A	A	mist.Sod Sal.	3	8	
5.	Foote	F	17	2	7	98	A	A	A	A	P	A	A	mist.Tuss. -Syr.Calcidrine	1	8	
6.	Osborne	F	52	3	1	100	P	P	A	P	P	P	P	mist.Bism. -mist.Pot.Iod.	5	14	Chronic Bronchitis.
7.	Nicholas	M	62	3	1	99	P	A	A	A	P	A	A	mist.Tuss -mist Strych Ac.	1	11	
8.	Norley	M	35	4	1	99	P	A	A	A	P	A	A	mist.Sod Sal. -mist Bark.	5	11	
9.	Hicks	F	45	5	3	101	P	P	A	P	P	A	A	mist.Tuss. -miat Strych.Ac.	2	5	
10.	Houston	F	45	7	1	100	P	P	A	P	P	A	P	mist.Tuss.-mist Scill. Co-Syr.Coc.	9	20	
11.	Elphick	F	65	11	1	100	P	P	A	A	P	A	P	mist.Sod Sal.-mist Bark.	5	14	Rheumatic.
12.	Larner	F	50	11	2	99	P	A	A	A	P	A	A	mist.Sod.Sal.	2	7	
13.	Crankshaw	F	43	16	1	101	P	P	A	A	P	A	A	mist.Tuss -mist Scill.Co.	4	10	
14.	White	M	50	13	1	99	P	P	A	A	P	A	A	mist.Tuss -mist Pot.Iod.	5	10	
15.	White	F	45	13	7	99	A	P	A	A	P	A	P	mist.Scill Co -mist Fer.Cit.	5	14	Anaemic.
16.	White	M	10	18	1	98	A	A	A	A	P	A	A	mist.Tuss.	4	7	
17.	Grimwood	F	50	13	1	99	P	P	A	P	P	A	A	mist.Tuss.-mist Pot.Iod.-S.Calc.	7	21	Chronic Bronchitis.
18.	Wilkinson	M	20	16	1	100	P	P	P	P	P	A	A	mist.Tuss. -mist Bark.	4	8	
19.	Owen	M	52	19	1	98	A	A	A	A	P	A	A	mist.Tuss	1	6	
20.	Gitsham	F	56	28	1	99	P	A	A	A	P	A	A	mist.Sod Sal-mist Scill.Co.	4	10	
21.	Welsh	F	50	31	2	100	P	A	A	A	P	A	A	mist.Tuss -mist Scill.Co.	6	14	
22.	Hughes	F	49	27	2	99	P	P	A	P	P	A	A	mist.Tuss -mist Strych Ac.	2	6	
23.	Bennett	M	38	27	1	101	A	A	A	A	P	A	A	mist.Tuss.	2	6	
24.	Crowhurst	M	54	3Aug.	1	98	P	P	A	A	P	A	A	mist.Tuss-mist Bark-S Coccil.	4	12	
25.	Clohesy	M	21	5	1	99	P	A	P	A	P	A	A	mist.Sod Sal.	4	7	
26.	Robey	F	52	6	2	99	P	A	A	P	P	A	A	mist.Tuss -mist Scill.Co	2	8	
27.	Pudney	F	45	8	2	99	P	A	A	A	P	A	A	mist.Tuss -mist Scill.Co	2	10	
28.	Hughes	F	46	8	1	100	A	P	A	A	P	A	A	mist.Tuss -mistFerr.Per.	3	7	Anaemic.
29.	Gardner	F	21	10	2	100	A	P	P	P	P	A	A	mist.Tuss. -mist Scill.Co	3	10	
30.	Marshall	M	63	10	3	99	P	P	A	A	P	A	A	mist.Sod Sal.- mist Bark.	4	9	

A = Symptoms absent
P = Symptoms present.

No.	Name.	Sex.	Age.	Date.	Days ill before seen.	Temperature	Musc.Pains	Headache	Coryza	Throat	Cough	Gastric	Nervous	Treatment.	Days till temp. norm. -better.	Days till cured.	Remarks.
31.	Reid	M	75	5Jly.	2	103	P	P	A	A	P	A	P	M&B 693.-mist.Strych.Ac.	2	40	Very ill.Str.hypos.6hrly.
32.	Woolford	M	61	6	1	98	P	P	A	A	P	A	A	Sulphanilamide	2	7	
33.	Polkimghorne	F	17	6	1	101	P	P	A	A	P	A	A	Sulphanilamide	1	4	Three months pregnant.
34.	Staples	F	86	6	1	97	P	P	A	A	P	A	A	Sulphanilamide.-Syr.Cocc.Co- (-mist Str.AC.	2	14	Chronic bronchitis.
35.	Kirkbride	M	70	6	2	99	A	P	A	A	P	A	A	Sulphanilamide	2	7	
36.	Kirkbride	F	69	6	2	98	P	A	A	A	P	A	A	Sulphanilamide	2	7	
37.	King	M	35	6	1	99	P	A	A	P	P	A	A	Sulphanilamide	2	4	
38.	Tremby	M	23	6	1	99	P	A	A	P	P	A	A	Sulphanilamide	2	6	
39.	Slater	M	50	7	1	99	P	P	A	P	P	A	A	Sulphanilamide	2	7	
40.	Spriggs	F	24	7	1	101	P	A	A	P	P	A	A	Sulphanilamide.-Syr Calc.	2	5	Asthmatical.
41.	Stockley	M	60	7	1	98	P	A	A	P	P	A	A	Sulphanilamide	2	4	
42.	Gaston	M	30	8	2	100	P	A	A	A	P	A	A	Sulphanilamide	2	5	
43.	Herren	F	81	8	2	102	P	P	A	P	P	A	P	M&B 693.-mist Strych.Ac.	2	24	Strych.hypos. 6 hrly.
44.	Houston	F	10	9	1	98	P	P	A	A	A	A	A	Sulphanilamide	1	3	
45.	Martens	M	60	7	2	103	P	P	A	P	P	A	P	M&B 693.-mist Paraldehyde.	4	10	Asthma and chronic bronch.
46.	Pope	M	6	8	1	103	P	P	A	A	P	A	A	Sulphanilamide	1	4	
47.	Green	F	45	7	1	100	P	A	A	P	P	A	A	Sulphanilamide	2	7	
48.	Webb	F	18	11	1	99	P	P	A	A	A	A	A	Sulphanilamide	5	9	
49.	Godden	M	30	12	1	101	P	P	A	P	P	A	A	Sulphanilamide.-mist Bark.	5	13	Relapsed.
50.	Brown	F	45	13	2	101	P	P	A	A	P	A	A	Sulphanilamdie	5	8	
51.	Meaney	M	4	21	1	99	A	P	A	A	P	A	A	Sulphanilamide	1	7	
52.	Kemp	M	8	22	1	102	P	P	A	P	P	A	A	Sulphanilamide	1	3	
53.	Kemp	F	3	22	1	99	A	A	A	A	P	A	A	Sulphanilamide	1	7	
54.	Prince	F	4	22	7	102	P	P	P	P	P	P	A	Sulphanilamide	1	3	Ulcerated tongue etc .
55.	Goscombe	F	8	22	1	101	P	P	A	P	A	A	A	Sulphanilamide	2	6	
56.	Kollasche	M	71	27	1	102	P	P	A	A	P	A	A	M&B 693 -mist Strych.Ac	1	12	Chronic bronchitis.
57.	Westley	F	26	31	1	102	P	P	A	A	P	A	A	Sulphanilamide	1	4	Eight months pregnant.
58.	Pople	F	45	1Aug.	1	104	P	P	A	P	P	A	A	Sulphanilamide.-mist Pot.Iod.	1	10	Cough troublesome.
59.	Webber	M	66	5	4	102	P	P	A	A	P	A	P	M&B 693.-mist Strych.Ac.	1	10	Hypos Adr.Str.&Atropine.
60.	James	M	14	5	1	99	P	A	A	P	P	A	A	Sulphanilamide.	3	7	

Duration of primary pyrexia.

Days	1	2	3	4	5	6	7	-14
Control group	3	6	3	8	6	1	2	1
Sulphanilamide group	11	14	1	1	3	0	0	0

Duration till free of symptoms and able to get up.

Days	3	4	5	6	7	-10	-14	-21	over 21
Control group	0	0	1	3	5	10	8	3	0
Sulphanilamide group	3	5	2	2	8	5	3	0	2

From the above comparison it appears that the group treated with sulphanilamide did better than the group treated with ordinary medicines. This applies both to duration of the primary pyrexia, when the patients were full of complaints and had not, as it were, "turned the corner", and to the duration of the complete illness. It must be remembered that the worst cases were given sulphanilamide, which accounts for the length of the illness in two of the sulphanilamide group being over 21 days. I am sure in my own mind that these two cases would not have lived had it not been for M & B 693.

It seems, then, that in treating influenza we have found that ordinary drugs have no specific action, no matter how thay are given, and are of little use except to relieve certain of the discomforts that accompany any fever. (15.21.22)
Vaccines of the secondary invading organisms have fallen into disrepute, possibly because in the presence of the intense depression of the body caused by the virus the immunity they confer is overcome easily, whereas when M & B 693 is given the secondary invaders are rendered (45) harmless by direct action on themselves and thus the body is able to turn the whole of its resistance to fighting the virus.
Before long it is to be expected that research will enable us to have a polyvalent vaccine in use against (47) the virus in all its strains and, with the help of cor- (51) roboration of the work done in the periodicity of the epidemics and pandemics of influenza, we will know at what times this vaccine will be best used. (20)
Along with this we will have the derivatives of sulphanil- amide to deal with the secondary invading organisms. (23)
Gargling with antiseptics, particularly with some such (9) gargle as dilute ammon sulphate, which is said to have a specificity for the virus, and the wearing of gauze masks of five layers thickness will also help to (8) prevent the introduction of the virus. After its introduct- ion, the virus, like the modern tank borne infantryman is apparently protected from attacks of drugs, sera and chemicals whether given intravenously or not, because of its essential cytotropic characteristics, and so we can hope for no help from those.

Summary.

The etiology, clinical picture, and treatment of influenza up till the discovery of sulphanilamide has been recounted. Sulphanilamide and its derivatives discussed.
A comparison made of the use of sulphanilamide and ordinary drugs in some sixty cases of influenza which occurred in Adelaide this year and a final conclusion arrived at that the treatment of influenza should comprise the following six main points.

1. The wearing of a mask of five layers of gauze for all who are in contact with influenza. (8)
2. Gargles and mouth washes, especially of dilute ammon. sulphate to prevent introduction of virus. (9)
3. Adequate rest in bed.
4. Ordinary drugs as required for special symptoms.
5. Prophylactic vaccines of the virus in all its strains as soon as available, given at correct times to have maximum protection when epidemic is due. (47.51) (20)
6. M & B 693 to deal with the secondary invading organisms. (23)

The different prescriptions used in treatment.

Mist Bark.

Tinct Cinchonae.		m15
Tinct Nucis vomicae		m 5
Ammon Carb		gr 5
Aqua Chlorof.	ad	Oz½

Mist Bism.

Bism.Carb.		
Magn.Carb.	aa	gr 10
Sod.Bicarb.		
Aq. Chlor	ad	Oz½

Mist Ferr. Cit.

Ferri et Ammon cit.		gr 30
glycerine		m 30
aq chlor	ad	Oz½

Mist Ferr. perchlor.

Liq. ferri perchlor		m15
pot chlorate		gr 7½
glyc.		m30
aq. chlor	ad	Oz½

Mist Pot Iodide.

Pot Iodide		gr 5
ammon carb		gr 5
tr nuc vomic		m 5
vin ipecac		m10
tr camph co		m20
aq chlor	ad	Oz½

Mist Scillae Co.

Oxymel scillae		m 40
acid ipecac		m 10
tr camph co		m 20
aq chlor	ad	Oz ½

Mist Sod Sal.

Sod sal.		gr 10
pot bicarb		gr 10
ammon carb		gr 5
chlorodyne'85		m 10
aq. chlor	ad	Oz ½

Mist Strych acid

Liq strych hyd		m 5
ac hyd. dil		m 10
inf gent conc		m 20
aq chlor	ad	Oz ½

Mist Tussis.

Liq ammon acet conc		m 20
pot nitrate		gr 10
vin ipecac		m 10
tinct camph co		m 20
syrup tolut.		m 20
aq chlor	ad	Oz ½

Mist Paraldehyde

Liq ammon acet conc		m 20
pot nitrate		gr 10
vin ipec		m 10
tinct camph co		m 20
paraldehyde		m 20
ext glycyr liq		m60
aq chlor	ad	OZ ½

Syrup calcidrine (Abbott)
Syr codeia B P.
Syr Coccillana co(Parke Davis)

Inj.Atropine 1/100
Inj.Strychnine 1/60
Inj. Adrenaline 10mins.
M & B 693 tablets .5 grm.
Sulhanilamide tablets .5grm.
(any brand)

REFERENCES.

1.Boyd,Text book of pathology (2nd edition) 235.
2.Francis T.Jnr. 1934 Science 80.457.
3.Burnet F.M. 1935 Med Jour.Australia 2.651.
4.Smorodintseff A.A.et alia 1936 Lancet 2 1383.
5.Smith and Stuart-Harris C H. 1936 Lancet 2 121.
6.Shope R.E. 1936 Medicine 15.453.
7.Stuart-Harris,Andrewes and Smith 1938 M.R.C.R.Ser No 228.
8.Hurst,E.Weston Lecture on virus diseases Adelaide Aug 1939.
9.Capisarow M. Edin Med J. 1939 Jan.
10.Boyd Text book of pathology p236.
11.Tulloch W.J. Edin Med.J. 1939 125.
12.Boyd Text book of pathology 126.
13.Beaumont G.E. Text book of Medicine (3rd edition) p563.
14.Price F.W Text book of Medicine. (4th edition) p137.
15.Scadding J.G. Practitioner 1938 Dec. p 712 etc.
16.Scadding J.G. 1937 Quart J.Med 6.425.
17.Laidlaw,Smith Andrewes&Dunkin 1935 B.J.Exp Path 16 275.
18.Andrewes C.H. 1937 B.M.J. 2.513.
19.Magill & Francis 1936 Proc S.E.Biol N.Y. 35 423.
20.Webster J.H.D 1939 Edin M.J. p 598.
21.Price F.W Text book of Medicine. pp142 143
22.Beaumont. Medicine. p 566.
24.Arganat,Dreosti &Ordman 1939 Lancet 1 309 380.
23.Buttle G.A.H B.M.J. 1939 pp 269.
25.Evans G.M & Gaisford 1938 Lancet 2 14.
26.McKeith & Oppenheimer 1939 Lancet 1 1099.
27.Raman P.S. 1939 Lancet 1 1101.
28.Reid G.C.K and Dyke 1938 Lancet 2 667.
29.Robertson K. 1938 Lancet 3 728.
30.McLean,Rogers & Fleming 1939 Lancet 1 562.
31.Bliss & Long. 1939 Proc. S.E.Biol N.Y. 1 566.
32.Whitby L.E.H. 1938a Lancet 1 1210.
33.Fenton & Hodgkiss 1938 Lancet 2 667.
34.Bryant & Fairman 1939 Lancet 1 923.
35.Somers & Usher 1939 Lancet 1 921.
36.Whitby . 1938 b Lancet 2 1095.
37.Marshall,Emerson & Cutting. 1937 a J.Amer M.Assoc.108 953.
38.Banks H.S 1938 Lancet 2 7.
39.Hansen L. 1939 J.Pharm 65 372.
40.Marshall,Emerson & Cutting 1937b J Phar. 61 191.
41.Marshall E.K Jnr. 1939 Phys Rev. 19 240.
42.Marshall,Bratton & Litchfield 1938 Sc. 88 597.
43.McIntosh & Whitby 1939 Lancet 1 431.
44.Fuller & Maxted.Brit.J.Exp Path vol20 177.
45.Oag,R Knight. Edin M.J. 1939 p 554.
45. Royal Soc Trp Medicine&Hyg. B.M.J.1939 p 84.
46.Tulloch Edin M.J. 1939 p 125.
47.Hogarth J.C. B.M.J. 1939 718
48.Anderson S. B.M.J. 1939 716.
49.Atkinson N. Bact Dep. Adelaide Hosp.(by word).
50.Southwood A.R. M.O.H. Adelaide circular July 13th 1939.
51.Stuart-Harris B.M.J. 1939 p 411.